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Osteogenic Sarcoma in the Rothmund-Thomson Syndrome

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Two children who had the Rothmund-Thomson syndrome and developed osteosarcoma are reported. The 10 previously reported cases are reviewed. The osteosarcomas developed at a younger age than normally expected and 66% occurred in the tibia/fibula. Four of the five patients for whom information was available showed undue sensitivity to cancer chemotherapy agents with prolonged myelosuppression and severe mucositis. It is recommended that doxorubicin in particular should be given with extreme caution in such patients. © 1996 Wiley-Liss, Inc.

Key words: osteogenic sarcoma, Rothmund-Thomson syndrome

INTRODUCTION

Rothmund-Thomson syndrome (RTS) is a rare condition of unknown aetiology characterised by poikiloderma. The literature reports 200 cases [1]. The disorder is inherited in an autosomal recessive fashion. The disease was first described by Rothmund in 1887 as an erythematous rash associated with cataracts [2]. Similar skin findings associated with developmental bone abnormalities of the forearms and hands, without cataracts, were subsequently described by Thomson in 1923 [3] and again in 1936 as poikiloderma congenitale [4]. In 1957, in reporting a case and reviewing the literature, Taylor [5] concluded that Rothmund and Thomson had described the same condition.

The clinical features of RTS, in descending order of prevalence, include early onset of poikiloderma, short stature, absence or sparseness of eyebrows and eyelashes, juvenile cataracts, small hands and bone defects, sunlight sensitivity, hypogonadism, defective dentition, nail abnormalities, and hyperkeratosis. The poikiloderma is not congenital but develops in the first year of life and is characterised by dermal atrophy associated with telangiectasia, hyperpigmentation, and depigmentation. The affected skin is soft and pliable, and the changes particularly affect the cheeks, buttocks, and extensor surfaces of the hands, forearms, and legs. Osteosarcoma was first reported in association with RTS in 1962 [6], although it was not until 1990 that it was suggested to be more common than expected [7]. Since then, a further nine cases have been described [8–16]. We report another two cases and review the literature with particular regard to the tolerance of RTS patients to cytotoxic chemotherapy.

CASE REPORTS

Case 1

The patient is the third child of nonconsanguineous parents with no relevant family history. He presented with "facial eczema' at the age of 5 months and with failure to thrive 2 months later. He developed the characteristic skin lesions of RTS at the age of 8 months, and the diagnosis was supported by a skin biopsy taken at the age of 19 months. He was a small slim boy, whose height and weight had progressed just below the third centile. He had the characteristic telangectatic rash, particularly marked on the face, (Fig. 1), ear margins, forearms, back of hands, buttocks, and lower legs but not on the tops of the feet. He had no cataracts and no demonstrable endocrine abnormalities. His scalp hair, eyebrows, eyelashes, fingernails, and dentition were all normal, as was his intelligence. Urinary excretion of mucopolysaccharides was normal.

A skeletal survey performed at the age of 5½ years showed a developmental defect affecting the medial aspect of both proximal tibial metaphyses and mild genu valgum. There was also noted to be a slight prominence of the longitudinal trabeculae in the long bones (Fig. 2a).

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Fig. 1. Facial appearance of Case 1, age 9 years.

Fig. 2. Radiograph of right tibia of Case 1 showing abnormal bone texture and shape at 5 years **(a)** and osteosarcoma at age 9 years **(b)**.

He presented at the age of 9 years in 1992 with a 6-day history of pain and swelling of his right leg below the knee. Examination revealed a tender bony mass, 5 cm in diameter, on the medial aspects of the proximal tibia. A biopsy confirmed the radiological interpretation (Fig. 2b) of a high-grade medullary osteogenic sarcoma and a chest X-ray showed one small possible pulmonary metastasis. The bone marrow was abnormal, showing a possible megaloblastic dyserythropoiesis, the exact nature of which remains unclear. Although low grade anaemia had been reported in connection with Rothmund-Thomson syndrome [7], there has been no previous report of megaloblastic dyserythropoiesis.

He was treated with chemotherapy consisting of three pre- and three postoperative courses of cisplatin and doxorubicin given every 2–3 weeks with the addition of granulocyte colony-stimulating factor. He tolerated the chemotherapy poorly with frequent episodes of oral and oesophageal ulceration, severe nutritional problems, weight loss, and frequent infection. In spite of this, surgery was undertaken at week 9 as planned. Initial surgery was a rotationplasty, but this was later converted to a midthigh amputation. The dose of doxorubicin had to be successively reduced until he was on only 41% of the initial target dose even allowing for his reduced surface area on the final course of chemotherapy. There was no unexpected renal toxicity, his GFR following treatment being 135 ml/min/1.73m^2. Repeat chest X-rays were normal and he remains well 30 months after the original presentation of the tumor. His poikiloderma improved dramatically while on chemotherapy but has now returned to the former appearance. Two years after completion of chemotherapy, he has a normal blood count and film. Bone marrow examination has not been repeated so we are unable to reassess the megaloblastic dyserythropeiesis.

Case 2

A 10-year-old boy presented in 1977 with a 7-week history of a painful wrist. A biopsy of the radius showed this to be a high-grade medullary osteosarcoma. He had previously been diagnosed as suffering from RTS. The tumour was treated by above elbow amputation followed by chemotherapy with doxorubicin, cyclophosphamide, and methotrexate. He tolerated the chemotherapy poorly in spite of surface area related dose reduction with prolonged periods of neutropenia resulting in extended gaps of 4–5 weeks between courses of chemotherapy. Four months after diagnosis, he developed pulmonary metastases, and he died 10 months after diagnosis.

DISCUSSION

Previous reports have demonstrated a clear association between RTS and the development of osteosarcoma (OS) [7]. Ten previous cases have been reported, and we have added two more out of a total of only 200 cases of RTS. The characteristics of these 12 cases are shown in Table I.

TABLE I. Review of World Literature on Osteosarcoma and RTS

Year	Author[a]	Age	Sex	Site	Assoc. bone lesions	Treatment[b]	Chemo. tolerance	Outcome[c]	Comments
1962	Roschlau [6]	12	M	Femur	NK	NK	NK	NK	
1976	Tokunaga [8]	19	F	Tibia	Yes	Chemo	NK	6 yr, D	Parents are cousins.
1980	Kozlowski [9]	13	M	Tibia	Yes	Chemo	NK	A/W 14 yr	
1982	Dick [10]	5	F	Tibia	NK	Chemo	NK	6 mo, D	
1985	Rebaud [11]	11	M	Tibia	NK	NK	NK	D	Parents are cousins.
1989	Baro [12]	18	F	Calcaneum	Yes	No chemo	—	D	
1989	Varughese [13]	11	F	Tibia	NK	MTX/CDDP/DOX	Normal	A/W	Developed second primary osteosarcoma
1992	Sim [14]	15	F	Tibia/humerus	NK	IFO/DOX/MTX	Poor	?	
1993	Drouin [15]	11	M	Femur	Yes	T10	NK	?	
1993	Judge [16]	10	F	Fibula	Yes	CDDP/DOX	Poor	A/W 2 yr +	
	Leonard	9	M	Tibia	Yes	CDDP/DOX	Poor	A/W 2 yr +	
	Leonard	10	M	Radius	NK	VCR/MTX/CYCLO	Poor	10 mo, D	

[a]Reference no. in brackets.
[b]NK = not known; MTX = methotrexate; CDDP = cisplatin; DOX = doxorubicin; IFO = Ifosfamide; T10 = multidrug Rosen protocol; VCR = vincristine; CYCLO = cyclophosphamide.
[c]D = deceased; A/W = Alive and well.

The clinical presentation of OS in these patients differs in several aspects from that of isolated OS. The equal sex ratio corresponds to that of RTS where 51% were female compared to a usual excess of males in OS. The age of presentation ranged from 5 to 19 years with a median of 11 years, which is somewhat lower than that normally seen in osteosarcoma. The younger age at presentation is consistent with a genetic predisposition to cancer as also seen in the Li Fraumeni syndrome [17]. The site of the OS in patients with RTS is usually below the knee with only one solely in the upper limb, again differing from that reported. In large series it is usually reported that equal numbers are just above or below the knee. One of the tumours was multicentric at presentation [14] and one [13] has subsequently developed a secondary primary osteosarcoma 2½ years after the initial presentation (Anne O'Meara, pers. comm.). Half of the previously reported patients had pre-existing abnormal bones as did the first case presented here. The majority of osteosarcomas occurring in young people do so in apparently previously normal bone. However, there have been reports of the development of osteosarcoma in abnormal bone such as traumatic bone injury [18], irradiated bone [19], and inherited bone dysplasia [20]. RTS is thought to be inherited in an autosomal recessive manner, and this is supported by two of the 12 reported cases having parents who were first cousins.

There have also been reports of other malignancies in patients with RTS [1]. Eight have had cutaneous malignancies, the youngest being at age 14 years, most of the remainder occurring in young adult life sooner than would be expected in normal individuals. In addition, there have been individual reports of fibrosarcoma, parathyroid adenoma, Hodgkin's disease, gastric carcinoma, and more recently malignant fibrous histiocytoma [22]. The pathogenesis of osteosarcoma in general is unknown, but in the case of RTS a major genetic component is likely. In both Li Fraumeni and Werner's progeria syndromes' there is an excess of osteosarcoma as well as soft tissue sarcoma and other tumours [21]. The study of unusual associations of syndromes and cancers may well lead to the discovery of pathogenetic mechanisms that are common to many more common tumours.

Chemotherapy now plays a vital role in the management of osteosarcoma in young people. There have been suggestions of an inherent DNA repair defect in patients with RTS, although reports are conflicting and no consistent abnormality has been demonstrated [1]. As a consequence, there is the possibility that patients with RTS treated with anticancer chemotherapy might show undue sensitivity to the agents used. In the five reported cases, where it is possible to obtain some information relating to this, four showed abnormal sensitivity with prolonged periods of myelosuppression and severe mucosal ulceration. These led to considerable prolongation of the intervals between courses of chemotherapy and reduction in the doses of drugs given. When giving combinations of drugs, it is not possible to determine with certainty which, if any, is causing the most problem, but the dose of doxorubicin was thought to be most important in the first case presented here. Cisplatin is relatively nonmyelotoxic and does not usually cause mucosal ulceration, its main toxicity being renal. There was no unexpected renal toxicity reported in any of the previous cases nor in the new ones.

The number of cases reported are insufficient to make conclusions regarding survival. Four of the eight where information is available remain alive and well.

It is concluded that there is a real association between RTS and osteosarcoma and there should be a high index of suspicion when patients with RTS develop bony pain. Patients with RTS may be very sensitive to the side effects of anticancer drugs, especially doxorubicin, which should be administered with caution, probably starting with a reduced dose.

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